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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/691,763 | 10/18/2000 | Paula M. Vertino | E0355/7003/ERG/MAT | 3870 |

7590 05/08/2002
Edward R. Gates
Wolf Greenfield & Sacks PC
600 Atlantic Ave
Boston, MA 02210

EXAMINER

GOLDBERG, JEANINE ANNE

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1634

DATE MAILED: 05/08/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/691,763

Applicant(s)

VERTINO, PAULA M.

Examiner

Jeanine A Goldberg

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5,13,21,30,38,47,58,61,67,68,71,72,95,101,105 and 110-124 is/are pending in the application.
- 4a) Of the above claim(s) 5,13,21,30,38,58,61,67,68,71,72,95,101 and 105 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,47 and 110-124 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 19, 20.
- 4) ☒ Interview Summary (PTO-413) Paper No(s) 21.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This action is in response to the papers filed January 18, 2002. Currently, claims 1, 5, 13, 21, 30, 38, 47, 58, 61, 67-68, 71-72, 95, 101, 105, 110-124 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
2. This action contains new grounds of rejection.
3. Any objections and rejections not reiterated below are hereby withdrawn.
4. The declaration by Paula Vertino and the arguments filed January 18, 2002, have been thoroughly reviewed. The declaration illustrates that the methylation of the TMS1 CpG island is present in not only breast tumors, breast cell lines, but also in primary human glioblastoma multiforme tumor samples, lung cancer cell lines and ovarian cancer cell lines. Therefore, enablement has been demonstrated to detect hypermethylation of the TMS1 CpG island of SEQ ID NO: 4 as indicative of cancer. Moreover, based upon the arguments and the data provided in the specification, the method for non-responsiveness to apoptosis-dependent anti-cancer therapy has been reconsidered and deemed enabled since the CpG island down-regulates expression of the TMS1 molecules and TMS1 has apoptosis inducing activity.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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5. Claims 1, 47, 110-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the level of methylation using SEQ ID NO: 4, the CpG island within the TMS1 nucleic acid does not reasonably provide enablement for correlating any nucleic acid which hybridizes to SEQ ID NO: 4 to indicate cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to methods of determining the level of methylation of a TMS1 CpG island using a nucleic acid which hybridizes under stringent conditions to a complement of SEQ ID NO: 4.

The specification teaches analyzing SEQ ID NO: 4 for increased methylation in cancer.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. Since the specification nor the claims specifically teach a definition for stringent conditions, the claim may be read very broadly to encompass nucleic acids which do not have the same function or activity as the TMS1 nucleic acid molecule which contains a CARD domain and which induces apoptosis. Therefore, as suggested in the interview of May 3, 2002, "A method for identifying a subject at risk of developing a cancer characterized by abnormally increased methylation of a CpG island containing TMS1 nucleic acid molecule comprising determining a level of methylation of a CpG island of a TMS1 nucleic acid molecule in a biological sample from a subject, and

comparing the level of methylation of the CpG island **of the** TMS1 nucleic acid molecule in the biological sample to a control wherein the CpG island **of the** TMS1 nucleic acid molecule is selected from the group consisting of

(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO: 4 and **wherein said TMS1 nucleic acid codes for a TMS1 polypeptide comprising a** caspase recruiting domain (CARD) and having apoptosis inducing activity, wherein the stringent conditions are 65° C and 3.5X SSC and

(b) complements of (a), and

wherein an increase in the level of methylation **of the** CpG island of the TMS1 nucleic acid molecule in the biological sample compared to the control identifies a subject at risk of developing the cancer.” The claim would provide both structure and function for the nucleic acid which is being analyzed. However, as written the claim does not have a definite structure nor function. While Claim 1 does require that the nucleic acid encode for a native TMS1 polypeptide, the specification does not teach how to identify a molecule is a TMS1 polypeptide either by assay or specific structure.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 47, 110-124 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 47, 110-124 are directed to nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO: 4. However, stringent conditions are a relative term which have different meanings to artisans in the art. The specification on page 19, provides some examples of stringent conditions, but does not specifically define the metes and bounds of stringent conditions. As discussed in an interview of May 3, 2002, the claim could be amended to recite "(a) nucleic acid molecules which hybridize under stringent conditions to a complement of a molecule consisting of SEQ ID NO: 4 and **wherein said TMS1 nucleic acid codes for a TMS1 polypeptide comprising a caspase recruiting domain (CARD) and having apoptosis inducing activity, wherein the stringent conditions are 65° C and 3.5X SSC**".

B) Claims 1, 47, 110-122 are indefinite because it is unclear whether the CpG island contains the TMS1 nucleic acid or whether the TMS1 nucleic acid contains the CpG island. As discussed in an interview of May 3, 2002, the claim could be amended to recite "CpG island **of the** TMS1 nucleic acid molecule".

Conclusion

7. **No claims allowable.**

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is

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(703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Pauline Farrier, whose telephone number is (703) 305-3550.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
May 6, 2002


W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600